REMARKS

The Examiner has objected to the specification because of references to previous studies.

The previous studies are applicants' own studies and are disclosed in U.S. Patent No. 6,156,725. This patent issued from U.S. Patent application 08/727,679. Page 1 of this application has been amended to insert - - now U.S. Patent 6,156,725 - - after the application number.

Therefore, it is respectfully requested that this objection be withdrawn.

The Examiner objects to the specification stating that the definition for Dxg includes Aib and based on this rejects claims 1-4 and 32-36 as being based on a specification which is found objectionable. This objection is respectfully traversed. In sequences claimed in claims 1, 2 and 32-36 some sequences include Aib, others include Dxg as a cyclic or acyclic dialkylated glycine and others contain both. Therefore, it is respectfully requested that this rejection be withdrawn.

The Examiner has rejected claims 1-4 and 32-36 under 35 USC 112, first paragraph. Applicants respectfully traverse this rejection.

The Examiner states that the specification does not disclose how to make and use the novel peptides. The Examiner states that the synthesis of alpha, alpha-disubstituted glycine or amino acids are difficult and cites page 291 of Spatola, Chemistry and Biochemistry of Amino Acids, Peptide and Proteins, Chapter 5. It is stated on page 291 of Spatola "In spite of synthetic difficulties [68], many new α,α-disubstituted amino acids are being produced [49] and will continue to be introduced as selective amino acid replacements. Reference [68] is G.C. Barrett, P.M. Hardy, T.A. Harrow and H.N. Rydon, J. Chem. Soc. Perkin I, 2634 (1972).

The references [49] date from 1977 and 1981. Since many α,α-disubstituted amino acids were being produced 5 years after the Barrett et al publication, one skilled in the art would assume that the difficulties, if any, referred to in Barrett had been overcome by 1977.

The peptides described in the present application can be synthesized using solid phase techniques. The methods for the chemical synthesis of

polypeptides are well known in the art (Stewart and Young, 1969, Solid Phase Peptide Synthesis, W.H. Freeman Co.).

In the present invention the following chemical moieties can be used to protect reactive side chains of the peptides during the synthesis procedure. The N-terminal amino group can be protected by 9-fluorenylmethoxycarbonyl (Fmoc) group. The hydroxyl groups of Threonine and Tyrosine can be preferably protected by t-butyl group (tBu). Leu, Met and Pro can be used unprotected. 2-8 equivalents of Fmoc protected amino acid per resin nitrogen equivalent can be used. The activating reagents used for coupling amino acids to the resin, in solid phase peptide synthesis, are well known in the art. These include BOP, PyBOP, HBTU, TBTU, HOBt. Preferably, DCC or DIPCDI/HOBt or HBTU/HOBt and DIEA can be used as activating reagents in the coupling reactions. (Castro, B., et al. 1975, Tetrahedron, Lett. 1219-1222; Knoor, R., et al. 1989, Tetrahedron Lett., 15, 1927-1930).

The protected amino acids can be either activated *in situ* or added in the form of preactivated esters known in the art such as N-hydroxy succinamide esters, pentafluorophenyl esters etc. The coupling reaction can be carried out in DMF, DCM or NMP or a mixture of these solvents can be monitored by Kaiser test [Kaiser et al., Anal. Biochem., 34, 595-598 (1970)]. In case of a positive Kaiser test, the appropriate amino acid can be re-coupled using freshly prepared activated reagents.

After the coupling of each amino acids, the amino-terminal Fmoc group can be removed using 20% of piperidine in DMFand then the peptide-resin can be washed with methanol and dried. The analogs assembled thus on solid phase can then be cleaved from the resin support by treatment with trifluoroacetic acid, crystalline phenol, ethanedithiol, thioanisole and de-ionized water from 1.0 to 4.0 hours at room temperature. The crude peptide can be obtained by precipitation with cold dry ether, filtered, dissolved, and lyophilized.

The resulting crude peptide can be purified by preparative high performance liquid chromatography (HPLC) using a C_{18} reverse phase column on a Preparative HPLC system using a gradient of 0.1% TFA in acetonitrile and water. The Acetonitrile is evaporated and the fractions can be lyophilized to obtain the pure peptide. The identity of each peptide can be confirmed by electron-spray /MALDI mass spectroscopy.

Therefore, given the knowledge of the art for peptide synthesis and the

specification one skilled in the art can prepare the novel peptides.

One skilled in the art can also use the novel peptides.

The use of cell lines to test for anticancer activity is well know in the art.

The National Cancer Institute, Bethesda, Maryland subjects all of its potential anticancer molecules showing promising activity in vitro on cell lines representative of in vivo models Br J Cancer. 2001 May 18; 84(10):1289-90 (Relationships between drug activity in NCI preclinical in vitro and vivo models and early clinical trials); Semin Oncol 1992 Dec; 19(6):622-38 (The National Cancer Institute; Cancer drug discovery and development program), Japanese J Antibiot 1977 Dec; 30 Suppl:35-40 (Antitumor screening procedures of the National Cancer Institute).

A database search of the National Library of Medicine was carried out to determine the relevance of cell lines used by the applicants for determining the anticancer activity of the peptides. HT29 (human colon) showed 1083 "hits" when searched with reference to cancer and the other human cancer cell lines used also showed a large number of hits (832 for A549, 727 for MOLT-4, 475 for DU145, 199 for HBI, 196 for SW620 and 77 for PA-1). This clearly shows the extensive use of these cell lines in cancer research. Further, it is a common and standard practice and norm for testing molecules showing promising anticancer activity *in vitro* to be tested in *in vivo* models.

Peptides of this invention were tested in the HT-29, SW620, PTC, PA-1,A549, HBL100, MOLT-4 and DU145 which represent colon, ovary, lung, breast, leukemia and prostate cancer. As explained above positive results in these tests will lead to further testing in vivo. The protocol results are given in Example 1 see Table 1 where SEQ IDS NO:2-9 (corresponding to DT-11 to DT-19 were tested).

Since the applicants have explained the protocol for testing the peptides of this invention *in vitro* and have established that these in vitro screening methods are used by those of skill in the art to determine anticancer activity and that positive results in these studies can lead to further in vivo testing and have shown how to use the claimed peptides in these assays, it is respectfully requested that this rejection be withdrawn.

The Examiner rejects claims 1-4 and 32-36 under 35 USC 112, second

paragraph. Applicants respectfully traverse this rejection.

Dxg is described in the specification. Therefore, it is not necessary to include a definition in the claims. It is respectfully requested that this rejection be withdrawn.

The Examiner rejects claims 1-4 and 32-36 under 35 USC 103(a). The Examiner states that claims 1-4 and 32-36 are obvious over Gozes (U.S. Patent 5,217,953) in view of Spatola in Chemistry and Biochemistry of Amino Acids, Peptides and Proteins, Chapter 5, page 271, 1983. Applicants respectfully traverse this rejection.

The Examiner states that Spatola teaches substitution of D amino acids for L amino acids. Spatola is a review paper and there is nothing in Spatola that discloses that the amino acids of VIP can be modified or replaced. Although, Spatola discloses use of D amino acids and Aib there is no disclosure or suggestion in Gozesor Spatola of the particular peptides claimed in this specification.

According to MPEP 2141 when applying 35 USC 103, the following tenets of patent law mus be adhered to:

> (A) The claimed invention must be considered as a whole; (B) The references must be considered as a whole and must suggest the desirability and thus the obviousness of making the combination; (C) The references must be viewed without the benefit of impermissible hindsight vision afforded by the claimed invention and (D) reasonable expectation of success is the standard with which obviousness is determined.

In making this rejection, the Examiner is relying on impermissible hindsight.

A reference must be considered for what it would teach someone skilled in the art at the time the invention was made and not be applied based on "hindsight". See Panduit Corp. V. Dennison Manufacturing Co. 227 USPQ 337, 343 (Fed. Cir. 1985):

> It is impermissible to first ascertain factually what applicants did and then view the prior art in such a manner as to select from the random facts of that art only those which may be modified and then utilized to reconstruct appellants' invention from such prior art.

In making its obviousness determination, a court must view the prior art without reading into that art the patent's teachings. Vandenberg v. Dairy Equipment, 224 U.S.P.Q. 195 (Fed. Cir. 1987) citing In re Sponnoble, 160 U.S.P.Q. 237 (CCPA 1969). In Uniroyal . Rudkin-Wiley, 50 U.S.P.Q.2d 1434, 1438 (Fed. Cir. 1988) the CAFC stated:

> The obviousness standard, while easy to expound, is sometimes difficult to apply. It requires the decision maker to return to the time the invention was made. The invention must be viewed not with the blueprint drawn by the inventor, but in the state of the art that existed at the time...That which may be clear and thus obvious to a court, with the invention fully diagramed and aided by experts in the field, may have been a breakthrough of substantial dimension when first unveiled [citations omitted]. In this case we are convinced that the district court misapplied the obviousness standard. It has impermissibly used hindsight to reconstruct the claimed invention from prior art with the invention before it and aided by Uniroyal's expert, rather than viewing the invention from the position of a person of ordinary skill at the time it was made. When prior art references require selective combination by the court to render obvious a subsequent invention, there must be some reason for the combination other than the hindsight gleaned from the invention itself.

Applicants respectfully draw the Examiner's attention to the table of contents on pages 267-268 of Spatola. Spatola lists 22 types of modifications that can be made to a peptide.

Given the numerous options provided in Spatola, the only basis for the Examiner's rejection is hindsight because there is no suggestion in either reference to modify VIP with a Dxg or Aib residue.

Therefore, it is respectfully requested that this rejection be withdrawn.

Applicants submit that the present application is in condition for allowance and favorable consideration is respectfully requested.

Respectfully submitted,

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In the Specification

Page 1, Paragraph 5. In U.S. Patent Application 08/727,679 now U.S. Patent 6,156,725, we have described the role of neuropeptides in cancer. High affinity and moderate affinity receptors for vasoactive intestinal peptide and somastostatin, high affinity receptors for bombesin and moderate affinity receptors for substance P were demonstrated on human colon adenocarcinoma cells. It was further demonstrated that peptide analogs to the above neuropeptides could actively and selectively induce cell death in the cancer cells. A formulation of peptide combination termed MuJ-& has also been described which causes tumor regression in xenotransplated nude mice. The individual constituent peptides of MuJ-7 were demonstrated to have anticancer activity.

In the Claims

Claim 1 (Amended) A peptide of the sequence Leu^1-Met^2-Tyr^3-Pro^4-Thr^5-Tyr^6-Leu^7-Lys^8 wherein at least one of the amino acids at positions 1-8 is replaced by Dxg (SEQ ID NO:1).